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The role of maternal serum alpha-fetoprotein in preterm birth: A literature review

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Abstract

Preterm birth is one of the most important global issues. Mortality and morbidity among children under 5 years, including neonates, is affected by preterm birth. A good maternal care, health workers, and health facilities play an important role in the outcome of pregnancy, including preterm birth. An early screening test for pregnancy is crucial to find any abnormality thus preterm birth can be predicted and the following treatment may be applied without delay. One of potential biomarker for the screening test is alpha-fetoprotein (AFP) that can be found in maternal serum. Web-based literature search was carried out using several keywords. This literature review aims to collect data and articles to conclude the correlation of the potential biomarkers in diagnostic of preterm birth.

Keywords: Preterm Birth; Alpha-Fetoprotein; Maternal Serum; Biomarker; Pregnancy

1. Introduction

Preterm birth is a world-wide problem with 15 million incidents per year [1]. Approximately 11% of total global births are preterm [2]. It contributes to mortality of children under 5 years, including neonates. It also accounted for 16% and 35% deaths of children under 5 years and neonates, respectively [3]. Some studies show that the mortality of neonates, especially in developing countries, is a result of an inadequate maternal care, insufficiency of health workers and health facilities, and the delayed abnormality detection prior to complications occur [4]. Therefore, an early detection of preterm birth is required to minimize the mortality and morbidity. Recent findings have shown a potential biological marker called alpha-fetoprotein (AFP) in maternal serum to be included in the early preterm screening test. The aims of this literature review are to elaborate the findings.

2. Materials and Methods

A literature exploration was performed using PubMed and ScienceDirect. The subsequent keywords were used: 'alpha-fetoprotein', 'preterm birth', 'maternal serum'. To maximize the findings, tracing was also carried out from the grey articles.

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3. Result and Discussion

3.1. Preterm Birth

A preterm infant is an infant delivered before 37 weeks of gestations. Based on the gestational age, preterm birth can be classified into extremely preterm (delivered before 28 weeks), very preterm (28 to 32 weeks), and moderate to late preterm (32 to 37 weeks) [5]. Approximately 85% preterm infants were delivered after 31 weeks of gestations [6]. Preterm birth has variety of short-term and long-term risks. A preterm infant can have neuromotor deficits, including slow development of motoric function, cerebral palsy, and brain injury. Sensorics and cognitive impairment can also be notified [7]. Another health aspects are also affected, such as respirational problems, hearing impairment, eye diseases, etc [6]. There are several risk factors of preterm birth, including idiopathic, iatrogenic, socio-demography, infection, and genetical factors. However, two thirds of preterm births occur in women without any risk factors [8].

3.2. Alpha-Fetoprotein

Alpha-fetoprotein is a protein produced by the liver and yolk sac during development of the fetal [9]. AFP's weight is approximately 70-kDa [10]. In mammals, AFP is classified as albuminoid gene superfamily, together with albumin, vitamin D (Gc) protein, and alpha albumin [11]. Alpha-fetoprotein is known as the regulator of growth in ontogeny and oncogenic. Alpha-fetoprotein serum binds and transports ligands, including bilirubin, fatty acid, retinoid, steroid, heavy metals, dyes, flavonoid, phytoestrogen, dioxin, and some drugs [12].

3.3. Alpha-Fetoprotein in Pregnancy

The amount of AFP in pregnancy is different according to its location. The synthesis of AFP will increase until 20th week of gestations and will be in constant level until the 32nd week. Subsequently, it will gradually decrease until the infant is delivered. Not only in the liver and yolk sac, but a small amount of AFP is also produced in gastrointestinal tract and fetal kidney. This protein will be shown in fetal serum 29 days after conception. The AFP will reach its maximum amount, approximately 3000-5000 g/mL, in the 10th to 13th week of gestations. It will decrease steadily due to dilutions as an effect of increase in fetal weight. When the infant is delivered, the concentration of AFP is approximately between 20 to 120 ng/mL, whereas in 32nd to 35th week, its concentration is estimated to reach 200-300 ng/mL. Albumin will replace AFP in the infants, specifically in the blood vessels.

In maternal serum, the AFP is detected at the 6th week of gestations and will continuously increase until 0.05 ng/mL in the second trimester. The highest concentration is approximately 1 ng/mL, can be seen in the 32nd week of gestations and will decrease by degrees until birth [13].

3.4. Alpha-Fetoprotein in Diagnostic of Preterm Birth

In predicting preterm birth, some studies use maternal serum AFP in the first and second semester as the biomarker for screening. After the collection of 13,828 women's AFP is taken by using enzym immunoassay (AutoDelfia AFP) in the second trimester, a study concluded that concentration of maternal AFP is related to an increase in the risk for preterm birth. The study revealed higher amount of AFP were found in maternal serum of preterm infants [14].

As aforementioned, AFP is known as the regulator of growth in ontogeny and oncogenic. AFP has similarity with albumin, but AFP is mostly arranged by protein that plays a role in increasing growth using cyclic-AMP protein kinase. However, growth process needs a good dynamic (up-and-down) regulation, in the same way as pregnancy. Fetal growth is highly important, but there is a period when fetus needs a temporary or prolonged growth cessation, such as differentiation, transformation, and a prevention of overgrowth in organs or tissues. Furthermore, fetus may have stress or shock insults in microenvironment compartments of fetal mileux. Thus, fetal growth in tissues or extracellular matrix may need to be temporarily stopped until the fetus reach homeostasis condition [12]. Stress or shock in fetus can cause a conformation change in AFP's molecule. This is the underlying reason that maternal serum AFP will increase in pathologic condition during pregnancy [15].

The correlation between an excessive increase in AFP and the possibility of preterm birth is through an impaired in placental perfusion and ischemia due to stress or shock conditions in fetus. This condition leads to placental impairment so that the amount of AFP in the serum will increase. Consequently, preterm birth may occur [16]. This situation is not related with an increase in fetal AFP-production, but an increase in leakage from fetal to maternal due to the impairment or dysfunction in placenta [13]. Some studies have shown several complications of pregnancy that are highly related to the placental dysfunction, such as preeclampsia, intra-uterine growth retraction, placental abruption, fetal death, and

spontaneous preterm birth [12]. Some conditions, such as fetal malformation, including neural tube defects (NTD) can also affect the amount of AFP [16].

Screening test of maternal serum AFP can be a good predictor even though risk factors can also help. The underlying cause of this statement is that the screening will be done in the early time of pregnancy. This potentially reduce the morbidity and mortality [17].

Some studies have concluded AFP as a potential biomarker in the screening test of preterm birth:

Table 1 Alpha-fetoprotein as a potential biomarker for preterm birth

No.	Studies	AFP cut-off (MoM)	Results
1	Jelliffe-Pawlowski LL, 2010 [18]	2.0	RR (95%CI) = 2.8 (2.6—3.1)
2	Alleman BW, 2013 [19]	2.5	OR (95% CI) = 6.99 (1.78—27.5) *P* value= 0.005
3	Tancrède S, 2015 [20]	2.0	RR (95% CI) = 4.6 (2.9—7.4)
4	Başbuğ D, 2017 [21]	2.0	OR (95% CI) = 5.547 (3.298—9.331)
5	Karya U, 2018 [22]	2.0	RR (95%CI) = 3.244 (1.66—6.337) *P* value = 0.0002
6	Hu JL, 2020 [23]	2.5	OR (95% CI) = 4.10 (2.44—6.88) *P* value = 0.000
7	Celik E, 2022 [24]	2.0	OR (95% CI) = 1.1 (0.4—3.1)

4. Conclusion

In further research, it is important to determine the exact time to do screening test using AFP as one of potential preterm birth biomarkers. Abnormalities that are detected earlier might have better outcome as the early and prompt treatment can be given.

Compliance with ethical standards

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Disclosure of conflict of interest

No conflict of interest.

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